Serial No.: 09/745,965
Attorney Docket: 3373.1

AMENDMENTS

Amendments to the Specification

Please replace the paragraph on page 7 (lines 9-22) with the following:

"Nucleic acids," according to the present invention, may include any polymer or oligomer of nucleosides or nucleotides (polynucleotides or oligonucletodies), which include pyrimidine and purine bases, preferably cytosine, thymine, and uracil, and adenine and guanine, respectively. See Albert L. Lehninger, PRINCIPLES OF BIOCHEMISTRY, at 793-800 (Worth Pub. 1982) and L. Stryer BIOCHEMISTRY, 4th Ed., (March 1995), both incorporated by reference. Indeed, the present invention contemplates any deoxyribonucleotide, ribonucleotide or peptide nucleic acid component, and any chemical variants thereof, such as methylated, hydroxymethylated or glucosylated forms of these bases, and the like. The polymers or oligomers may be heterogeneous or homogeneous in composition, and may be isolated from naturally-occurring sources or may be artificially or synthetically produced. See U.S. patent ~~application Serial~~ No. ~~08/630,427~~ 6,156,501 which is incorporated herein by reference in its entirety for all purposes. In addition, the nucleic acids may be DNA or RNA, or a mixture thereof, and may exist permanently or transitionally in single-stranded or double-stranded

Please replace the paragraph on page 9 (lines 1-22) with the following:

An "array" may comprise a solid support with peptide or nucleic acid probes attached to said support. Arrays typically comprise a plurality of different nucleic acids or peptide probes that are coupled to a surface of a substrate in different, known

locations. These arrays, also described as "microarrays" or colloquially "chips" have been generally described in the art, for example, U.S. Pat. Nos. 5,143,854, 5,445,934, 5,744,305, 5,677,195, 6,040,193, 5,424,186 and Fodor et al., Science, 251:767-777 (1991). Each of which is incorporated by reference in its entirety for all purposes. These arrays may generally be produced using mechanical synthesis methods or light directed synthesis methods which incorporate a combination of photolithographic methods and solid phase synthesis methods. Techniques for the synthesis of these arrays using mechanical synthesis methods, such as ink jet, channel block, flow channel, and spotting methods which are described in, e.g., U.S. Pat. Nos. 5,384,261, and 6,040,193, which are incorporated herein by reference in their entirety for all purposes. Although a planar array surface is preferred, the array may be fabricated on a surface of virtually any shape or even a multiplicity of surfaces. Arrays may be peptides or nucleic acids on beads, gels, polymeric surfaces, fibers such as fiber optics, glass or any other appropriate substrate, see U.S. Patent Nos. 5,744,305, 5,770,358, 5,789,162, 5,708,153, 6,040,193 and 5,800,992, which are hereby incorporated in their entirety for all purposes. Arrays may be packaged in such a manner as to allow for diagnostics or other manipulation of in an all inclusive device, see for example, US Patent Nos. 5,856,174 and 5,922,591, and 5,945,334, which are incorporated herein in their entirety by reference for all purposes. See also U.S. patent application Serial No. 09/545,207 (pending) which is incorporated herein in its

Please replace the paragraph on page 12 (lines 10-15) with the following:

Additional techniques for forming and using such arrays are described in U.S. Patent Nos. 5,384,261, and 6,040,193 which are also incorporated by reference for all purposes. Such techniques include systems for mechanically protecting portions of a substrate (or chip), and selectively deprotecting/coupling materials to the substrate. Still further techniques for array synthesis are provided in U.S. ~~Application No. 08/327,512~~ Patent No. 6,121,048, also incorporated herein by reference for all purposes.

Please replace the paragraph on page 14 (lines 1-8) with the following:

In one aspect of the invention, a physical model that is based on the thermodynamic properties of the sequence is used to predict the array-based hybridization intensities of the sequence. Hybridization propensities may be described by energetic parameters derived from the probe sequence, and variations in hybridization and chip manufacturing conditions will result in changes in these parameters that can be detected and corrected. Pending U.S. Patent Application Number 09/721,042, filed November 21, 2000 and incorporated herein by reference, discloses methods for predicting nucleic acid hybridization affinity.

Please replace the paragraph on page 15 (lines 9-12) with the following:

There are a number of ways to establish the relationship between the sequence and ΔG. In preferred embodiments, one model (equation 2), shown in pending U.S. Application Serial Number 09/721,042, filed on November 21, 2000, previously incorporated by reference is shown below:

Please replace the paragraph on page 17 (lines 5-14) with the following:

Hybridization intensities (relative to a reference base, such as an A) for each type of bases can be solved at each position in the probe sequence may be predicted. Multiple linear regression analysis is well known in the art, see, for example, the electronic ~~statistic~~ statistics book Statsoft, available on the World Wide Web; ~~(http://www.statsoftinc.com/textbook/stathome.html);~~ Darlington, R. B. (1990). *Regression and linear models*. New York: McGraw-Hill, both incorporated by reference for all purposes. Computer software packages, such as SAS, SPSS, and MatLib 5.3 provide multiple linear regression functions. In addition, computer software code examples suitable for performing multiple linear regression analysis are provided in, for example, the Numerical Recipes (NR) books developed by Numerical Recipes Software and published by Cambridge University Press (CUP, with U.K. and U.S. web sites).

Please replace the paragraph on page 19 (lines 1-7) with the following:

where W_d is the weight for sequence based probe affinity; W_{PF} is the weight for probe formation and W_{PP} is the weight for probe dimerization. Any methods that are capable of predicting probe folding and/or probe dimerization are suitable for at least some embodiments of the invention for predicting the hybridization intensity in at least some embodiments of the invention. In a particularly preferred embodiment, Oligowalk (available on the World Wide Web ~~at http://rna.chem.rochester.edu/RNAstructure.html, last visited Nov. 3, 2000~~) may be used to predict probe folding.

Please replace the paragraph on page 22 (lines 9-15) with the following:

In a preferred embodiment, the goal of the probe selection step is to find the best probes to represent a sequence. The probe selection software module takes a set of probes and a set of quality measures for each probe. It then implements an optimization algorithm to find the best n probes, spread out across the gene. Methods for probe selection using optimization algorithm is described in abandoned U.S. Provisional Application Number 60/252,617, filed November 21, 2000, and incorporated herein by reference in its entirety for all purposes.

Please replace the paragraph on page 24 (lines 1-4) with the following:

models) derived from experiment data (1311). In some embodiments, cross hybridization may also be evaluated by pruning probe sequences against a human genome data base (1312) which may be residing locally, in a local area network or in a remote site such as the Genbank ~~(http://www.ncbi.nlm.nih.gov)~~.